malignant mesotheliomas with osseous and cartilaginous differentiation after intraperitoneal injection of various types of mineral fibres in rats. Exp Toxic Pathol 1992;44:55-58).

Another issue concerning mesothelioma causation is whether the asbestos found in the lung or that translocated to the pleura is most important in causing mesothelioma. The carcinogenic (tumorigenic) agent responsible for causing a malignant neoplasm is thought to have to be in the immediate vicinity of where the tumor is located to be considered causative. Suzuki and Yuen discussed asbestos fiber types in the pleura and mesothelioma tumor tissue. They found the dominant fiber in pleural plaque and in tumor tissue to be chrysotile. This information suggests chrysotile is the most important factor in mesothelioma tumorigenesis (Suzuki Y, Yuen SR. *Asbestos fibers contributing to induction of human malignant mesothelioma.* Ann NY Acad Sci 2002; 982:160-176; and Suzuki Y, Yuen SR, Ashley R. *Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence.* Int J Hyg Environ Health 2005;208:201-210).

Boutin et al. suggest most pleural mesotheliomas arise in black spots on the parietal pleura where amphibole asbestos is concentrated (Boutin C, Dumortier P, Rey F, et al. *Black spots concentrate oncogenic asbestos fibers in the parietal pleura: thoracoscopic and mineralogic study.* Am J Respir Care Med 1996 Jan;153(1);444-449). With respect to black spots, Mitchev et al. stated it had been suggested the specific areas of the parietal pleura absorbed and retained inorganic particles from the pleural space, including carbon pigments and asbestos fibers, and could be starting points for pathologic changes induced by mineral fibers (Mitchev K, Dumortier P, De Vuyst P. *Black spots and hyaline pleural plaques on the parietal pleura of 150 urban necropsy cases.* Am J Surg Pathol 2002;26:1198-1206). The authors stated their purpose was to study the distribution of black spots, their microscopic appearance, and the possible relationship to pleural plaques in the parietal pleura of 150 consecutive necropsies of urban dwellers (mean age 67.7 ± 12.9 years) were examined. Black spots were stated to have been observed in 92.7% of the cases and were predominantly located in the lower costal and diaphragmatic zones and could correspond to the anatomic distributions of structures involved in pleural cavity clearance. Black spots correlated with sex (M > F) and age (old > young) and there was no relationship between the predominant locations of black spots and hyaline pleural plaques. The authors concluded black spots were present in the parietal pleura of the vast majority of the urban population and were more common in men and in elderly populations. The authors stated black spots were spread throughout the parietal pleura, but showed a topographic predominance on the paravertebral and axillary costal zones and in the diaphragmatic zones and could not be superimposed with the hyaline pleural plaques. The authors concluded the mechanisms of fiber migration and the exact pathogenic role of fiber characteristics in asbestos-related pleural disease remained opened.

Muller et al. reported on the results of the morphological and energy dispersive x-ray analysis of 12 black spots (4 surgical and 8 autopsy specimens) located in the parietal pleura (Muller KM, Schmitz I, Konstantinidis K. *Black spots of the parietal pleura: morphology and formal pathogenesis.* Respiration 2002;69:261-7). The authors stated black spots of the pleura developed in close correlation to lymphatic channels and blood vessels. Black spots were characterized by mild fibrosis and an inflammatory reaction to the incorporated foreign particles. The authors stated the connective tissue could result in the formation of hyaline granulomas. Aluminum, silicone and sometimes fibers were found in such areas. The authors concluded there were hints for an increased proliferation of mesothelial cells in some areas with black spots, although their findings did not support the classification of black spots as being an obligate early lesion in the development of malignant mesothelioma.

As reported by us in 1997, most patients have more than one type of asbestos in their lung tissue (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Path 1997;21:321-336). Amosite asbestos is the dominant fiber type found in the lungs of mesothelioma patients in the United States. Approximately 50% of patients have chrysotile in their lungs and the other 50% probably had chrysotile in their lungs but it was not identified due to clearance.

Mesothelioma summary:
1. Mesothelioma is a fatal cancer whose only epidemiologically known cause is exposure to asbestos fibers. The latency period for mesothelioma is between 10 and 70 years.
2. All types of asbestos fibers cause mesothelioma – there is no type of asbestos fiber which does not cause mesothelioma (WHO policy paper: *Elimination of asbestos-related diseases*).
3. Mesothelioma can be caused by very brief exposures to very low concentrations of asbestos fibers – there is no level of exposure below which mesothelioma cannot arise (Hillerdal G. *Mesothelioma: cases associated with non-occupational and low dose exposures.* Occup Environ Med 1999;56:505-513).
4. It is the cumulative exposure to asbestos which causes disease and, for this reason, any identifiable exposure to asbestos can cause or contribute to the development of mesothelioma.
5. Mesothelioma can arise from household or bystander exposure or in persons who work in occupations not typically associated with exposure to asbestos. (Joubert L, Seidman H, Selikoff IJ. *Mortality experience of family contacts of asbestos factory workers.* Ann NY Acad Sci 1991;643:416-418.)

LUNG CANCER

Lung cancer is the second major disease identified to be caused by asbestos. Lung cancer associated with asbestosis was first described in 1936 by Lynch and Smith (Lynch KM, Smith WA. Pulmonary asbestosis. III. *Carcinoma of the lung in asbestosis.* Am J Cancer 1936;14:56-64). Wedler found a high incidence of lung cancer among individuals in Europe who had been diagnosed with asbestosis (Wedler HD. Uber den Lungenkrebs bei Asbestose. Deut Med Woch 1943;69:575-576). Merewether also found an increased incidence of lung cancer and neoplasms referred to as "tumors of the pleura" (? mesothelioma) in asbestos factory workers compared to the non-asbestos exposed population (Merewether ERA. Annual Report of the Chief Inspector of Factories for the year 1947. London: His Majesty's Stationery Office 1949:78-81).

There are four issues that currently concern lung cancer and attribution to asbestos: 1) are there histologic types and specific locations of lung cancers that are more closely associated with asbestos exposure?; 2) what is the concentration of asbestos it takes to cause lung cancer and is there a threshold below which lung cancer will not occur at an increased incidence?; 3) is it necessary to have the disease asbestosis in an individual before lung cancer causation can be attributed to asbestos?; and 4) what is the relationship or interaction between asbestos and cigarette smoke carcinogens in causing lung cancer (synergism)?

All four major histological types of lung cancer (adenocarcinoma, squamous carcinoma, small cell lung cancer and large cell undifferentiated carcinoma) are observed in persons exposed to asbestos occurring at a rate similar to those in non-asbestos exposed individuals. The anatomic location of the neoplasm (upper lobe vs. lower lobe; peripheral vs. central) is not significant in determining whether a primary lung cancer is caused by asbestos. The issues of concentration of asbestos necessary to cause lung cancer and whether asbestosis is necessary to attribute lung caner causation to asbestos have been hotly debated. These issues have been extensively discussed by Henderson, et al. (Henderson DW, de Klerk NH, Hammar SP, et al. *Asbestos and lung cancer: is it attributable to asbestosis or to asbestos fiber burden?* Chapter 6. In: Corrin B, ed., Pathology of Lung Tumors. New York: Churchill-Livingstone, 1997:83-118). Three potential hypotheses were discussed: H1 – asbestos modifies lung structure so that fibrotic lung parenchyma becomes more prone to neoplastic transformation by carcinogens in tobacco smoke perhaps mediated by adjuvant effects of cytokines; H2 – lung cancer risk is increased only when the inhaled fiber burden falls into the range recorded for asbestosis; and H3 – any inhaled dose of asbestos has the potential to increase the risk of lung cancer. This author believes that inhaled dose is the most important factor in attributing lung cancer to asbestos exposure. Recent studies support the idea that asbestos concentration and not asbestosis is a critical factor for associating lung cancer to asbestos. Henderson et al. evaluated the published literature between 1997 and 2004 concerning lung cancer and asbestos and stated the prevailing evidence strongly supported the cumulative exposure model (Henderson DW, Rödelsperger K, Woidowitz H, Leigh J. *After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004.* Pathology 2004;36:517-550).

Cullen et al. concluded that among current and former smokers exposed occupationally to asbestos, the risk of lung cancer increase with increased exposure duration, even in persons without clinical evidence of asbestosis (Cullen MR, Barnett MJ, Balmes JR, et al. *Predictors of lung cancer among asbestos exposed men in the beta-carotene and retinol efficacy trial.* Am J Epidemiol 2005;161:260-270).

Reid et al. studied former workers and residences of Wittenoom with known amounts of asbestos exposure (Reid A, de Klerk N, Ambrosini GL, et al. *The effect of asbestosis on lung cancer risk beyond the dose related effect of asbestos alone.* Occup Environ Med 2005;62:885-889). Between 1990 and 2002 there were stated to have been 58 cases of lung cancer. The authors concluded there was an increased risk of lung cancer with increasing exposure in those without asbestosis and that asbestosis was not a mandatory precursor for asbestos-related lung cancer. The authors stated the findings supported the hypothesis that it was the asbestos fibers per se that caused lung cancer, which could develop with or without the presence of asbestosis. It has also become apparent that bilateral pleural plaques are associated with an increased risk for the development of lung cancer at a relative risk of 2. This probably does not have anything to do with plaques, but probably is related to the fact that people who have more plaques have higher asbestos concentrations in their lung tissue.

Exactly how much asbestos it takes to cause lung cancer is difficult to state. In 1986, Warnock and Isenberg (Warnock ML, Isenberg W. *Asbestos burden and the pathology of lung cancer.* Chest 1986;89:20-26) evaluated 75 men with primary lung cancer, most of whom had been exposed to asbestos. They found cases of individuals with pathologic asbestosis whose lung tissue contained as little as 100,000 amphibole asbestos fibers per gram of dry lung and suggested that if those men's lung cancer were related to asbestos, then those men's lung cancer whose lung tissue contained at least 100,000 amphibole asbestos fibers per gram of dry lung should also be causally related to asbestos.

Others have stated that a cumulative exposure of 25 fiber/cc years is estimated to increase the risk of lung cancer 2-fold, as is one year of heavy asbestos exposure or 5-10 years of moderate exposure. Finnish investigators have reported a 2-fold increase in lung cancer is related to a fiber level of 2 million fibers greater than 5 μm long per gram of dry lung tissue or 5 million fibers per gram of dry lung tissue greater than 1 μm long. This fiber concentration is stated to be approximately equivalent to 5,000-15,000 asbestos bodies per gram of dry lung tissue (500-1,500 asbestos bodies per gram of wet lung tissue).

Because chrysotile is cleared rapidly from the lung, tissue concentration values cannot be used to determine if lung cancer was caused by chrysotile. Fiber/cc/years is the best criterion for determining if chrysotile exposure was enough to cause lung cancer.

Henderson et al. reviewed literature between 1997 and 2004 concerning the issue of asbestos-induced lung cancer and pointed out a relative risk of less than 2 is indicative of a significant increase in lung cancer incidence and suggested that fiber year cumulative exposures less than 25 fiber cc years can be associated with a significant increase in lung cancer. They also discussed the issue of individual susceptibility (genetic susceptibility) that has the potential to cause an increased incidence of lung cancer at the same level of occupational exposure (Henderson DW, Rödelsperger K, Woidowitz H, Leigh J. *After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997-2004.* Pathology 2004;36:517-550).

The issue of synergism suggests cigarette smoke carcinogens and asbestos cause an increased incidence of lung cancer together that is greater than that caused by either one alone. The most often quoted study was by Selikoff, et al., (Selikoff EJ, Hammond EC, Churg J. *Asbestos exposure, smoking and neoplasia.* JAMA 1968;204:104-110) where they found there was an approximately 5-fold increase in the incidence of lung cancer in asbestos-exposed persons compared to non-smoking, non-asbestos-exposed workers; an 11 times increase of lung in cigarette smokers not exposed to asbestos; and an approximately 61-fold increase in the

incidence of lung cancers in persons who were cigarette smokers and occupationally exposed to asbestos.

The issue of synergism has been reviewed by Saracci who studied the interactions of tobacco smoking and other agents in the etiology of cancer. Saracci listed 13 studies evaluating this subject and came to the conclusion that in 10 of the 13 studies, there was evidence of multiplicative synergism between cigarette smoke and asbestos in causing lung cancer (Saracci R. *The interactions of tobacco smoking and other agents in cancer etiology.* Epidemiol Rev 1987;9:175-193). At this time, the only way that an individual can reduce their risk of developing lung cancer from asbestos is to stop smoking cigarettes and other tobacco products.

Lung cancer summary:
1. All types of asbestos fibers cause lung cancer – there is no type of asbestos fiber which cannot cause lung cancer.
2. It is the cumulative exposure to asbestos which causes disease and, for this reason, any identifiable exposure to asbestos can cause or contribute to the development of lung cancer provided the patient has been exposed to a sufficient dose of asbestos to attribute the lung cancer to the asbestos exposure. In my opinion, lung cancer can be attributed to asbestos exposure if the patient has one year of heavy occupational exposure to asbestos (e.g. shipyard workers and construction workers who were on site during the spraying of asbestos insulation) or five years of more moderate asbestos exposure (e.g. sheet metal workers and carpenters).
3. Lung cancer can be attributed to asbestos exposure even in the absence of radiologically detectable asbestosis.
4. Asbestos exposure combined with smoking is much more likely to increase the risk of developing lung cancer than either smoking or asbestos exposure alone.

OTHER CANCERS

With respect to other types of cancers caused by asbestos, it is this author's opinion that the ones associated with an asbestos etiology include laryngeal cancer, GI tract cancer and kidney cancer in individuals who are exposed to moderate to high amounts of asbestos (Greenberg SD, Roggli VL. *Other neoplasia*. Chapter 8. In: Roggli VL, Greenberg SD, Pratt PC. Pathology of asbestos-associated diseases. Boston: Little, Brown & Co., 1992:211-222). Three separate pathologic studies have shown an association between laryngeal cancer and parietal pleural plaques. The basis for attribution of non-pulmonary cancers to asbestos is based on the assumption that asbestos is translocated to the sites where these neoplasms occur. As reported by the Selikoff group, there is an increased relative risk of laryngeal cancer (relative risk 1.61-1.70), kidney cancer (relative risk 1.70-1.96) and GI tract cancers (relative risk 1.37-2.61).

With respect to lymphoma/myeloma/lymphocytic leukemia, there have been several case reports of these types of neoplasms associated with asbestos exposure. Asbestos translocates to lymph nodes and is reported to cause abnormalities in the immune system. An elevated number of lymphomas have been reported in persons exposed to asbestos as reviewed by Roggli and Greenberg (Greenberg SD, Roggli VL. *Other neoplasia*. Chapter 8. In: Roggli VL, Greenberg SD, Pratt PC, eds., Pathology of asbestos-associated diseases. Boston: Little, Brown & Co., 1992;211-222).

Several studies have shown an association between GI tract cancers and asbestos. Jansson et al. showed an association between the development of esophageal adenocarcinoma and exposure to asbestos with an incidence rate ratio of 4.5 (95%) and a confidence interval of 1.4-14.3 (Jansson C, Johansson AL, Bergdahl IA, et al. *Occupational exposures and risk of esophageal and gastric cardia cancers among male Swedish construction workers*. Cancer Causes Control 2005;16:755-764). Varga et al. stated the mechanism of cogenotoxic action between ingested amphibole asbestos fibers and benzo[a]pyrene via tissue specificity studies using comet assay showed high levels of DNA strand brakes in cells prepared from the omentum and intestine and demonstrated a significant potentiating effect of the absorbed carcinogen on the induction of DNA damage in omentum (Varga C, Horvath G, Timbrell V. *On the mechanism of cogenotoxic action between ingested amphibole asbestos fibres and benzo[a]pyrene: II. Tissue specificity studies using comet assay*. Cancer Lett 1999;139:173-176). Their results were stated to support the molecular model of asbestos carcinogenesis, including both asbestos-induced deletions and mutations caused by a mutagen carried by the same fibers.

Jakobsson et al. stated their aim was to investigate the association between exposure to mineral fibers and dust, and cancer in subsites within the large bowel. They found an increased incidence of cancer in the right colon in asbestos cement and cement workers. The distribution of cancers within the colon was stated to have been noticeably different from that in other blue collar workers, indicating their findings could not be explained by socioeconomic confounding factors alone (Jakobsson K, Albin M, Hagmar I. *Asbestos, cement, and cancer in the right part of the colon*. Occup Environ Med 1994;51:95-101).

With respect to head and neck cancers, Purdue et al. studied occupational exposures and head and neck cancers among Swedish construction workers and concluded there was an increased incidence of laryngeal cancers in asbestos-exposed individuals with a relative risk of 1.9 and a

confidence interval of 1.2-3.1 (Purdue MP, Jarvholm B, Bergdahl IA, Hayes RB, Baris D. *Occupational exposures and head and neck cancers among Swedish construction workers.* Scand J Work Environ Health 2006;32:270-275).

Wunsch studied the epidemiology of laryngeal cancer in Brazil and stated the most important risk factors involved in the genesis of laryngeal cancer were tobacco smoking and alcohol intake with other occupational exposures such as asbestos, strong inorganic acids, cement dust and free crystalline silica also being associated with the genesis of laryngeal cancer (Wunsch FV. *The epidemiology of laryngeal cancer in Brazil.* Sao Paulo Med J 2004;122:188-194).

Dietz et al. stated that investigators found that after adjustment for tobacco and alcohol intake, a significant elevated odds ratio could be demonstrated for persons that were exposed to cement during their work as building and construction workers (Dietz A, Ramroth H, Urban T, Ahrens W, Becher H. *Exposure to cement dust, related occupational groups and laryngeal cancer risk: results of a population based case-control study.* Int J Cancer 2004;108:907-911). The authors concluded there was good evidence that asbestos was an independent risk factor for laryngeal cancer.

Berrino et al. stated that significant elevated risk adjusted for nonoccupational variables (smoking, alcohol consumption and diet) and other occupational exposures were consistently found for organic solvents and asbestos (odds ratio 1.6, 1.0-2.5). The authors concluded that exposure to solvents was associated with an increased risk of hypopharyngeal/laryngeal cancer and their results provided additional evidence of an excess risk of hypopharyngeal/laryngeal cancer for exposure to asbestos (Berrino F, Richiardi L, Boffetta P, et al. *Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland.* Cancer Causes Control 2003;14:213-223).

Another study looking at occupational hazardous substance exposure and nutrition for pharyngeal and laryngeal carcinomas stated a case-control study to investigate occupational risk factors for squamous cell carcinoma of the oral cavity, pharynx and larynx was conducted (Maier H, Tisch M, Kyrberg H, Conradt C, Weidhauer H. *Occupational hazardous substance exposure and nutrition. Risk factors for mouth, pharyngeal and laryngeal carcinomas?* HNO 2002;50:743-752). The study included 209 male cancer patients and 110 male control persons without known malignant disease who were matched for age, alcohol consumption and tobacco consumption. The authors stated the educational level in the cancer group was significantly lower (17.2% of the cancer patients and 7.3% of the control persons) having not completed their professional training. An increased cancer ratio was observed for workers exposed to asbestos with an odds ratio of 8.7 (p = 0.004).

A committee on asbestos studied health effects regarding certain cancers and concluded the evidence was sufficient to infer a causal relationship between asbestos and laryngeal cancer (*Asbestos selected cancers.* Washington DC, National Academic Press 2006:187-188).

WR Grace Report

NON-NEOPLASTIC DISEASES CAUSED BY ASBESTOS

Non-neoplastic diseases caused by asbestos include asbestos-induced pleural effusion; hyaline pleural plaques; diffuse pleural fibrosis; round (rounded) atelectasis; pleural plaque spots; asbestosis; and localized and unusual benign conditions. Pathologic and other information concerning these conditions are discussed in detail in Chapter 27 of Pulmonary Pathology (Hammar SP, Dodson RF. *Asbestos.* Chapter 27. In: Dail DH, Hammar SP, eds., 3rd Ed. Pulmonary Pathology. New York: Springer-Verlag. *To be published in 2007*).

Asbestos-induced pleural effusion occurs primarily in older males who were often last exposed to asbestos 15 to 20 years prior to when the effusion occurred. The effusion is usually hemorrhagic and exudative and may be painful and is not infrequently associated with asbestos-induced hyaline pleural plaques and asbestosis. The effusion frequently contains a significant number of eosinophils. The effusion may last for weeks to several months and spontaneously resolve. Diagnosis of an asbestos-induced pleural effusion is somewhat a diagnosis of exclusion, since other conditions such as infection can cause a similar type of exudative effusion.

Hyaline pleural plaques are discrete, yellow-white, irregularly shaped, frequently calcified structures most frequently involving the parietal pleura and most frequently involving the parietal pleura covering the diaphragm and the parietal pleura in the posterior lower portion of the chest cavity. These structures are composed of dense fibrous tissue and frequently undergo calcification. Histologically, they show a basket weave pattern. They are almost always associated with elevated concentrations of asbestos in lung tissue and the plaques themselves contain asbestos fibers, the most common of which is chrysotile. In most instances, the plaques do not cause symptoms, although when they involve 50% or more of the parietal pleural surface, they can be associated with restrictive lung disease. The mechanism by which plaques develop is not well understood, but probably is related to localized inflammation caused by asbestos which then resolves. The exact time it takes for plaques to form is not known and the exact concentration of asbestos that it takes to form plaques is also not known, however, in general, there is a wide range of concentration of asbestos one finds in the lungs of people who have plaques.

Diffuse pleural fibrosis is relatively common in patients occupationally exposed to asbestos, although the exact incidence is not well documented. It occurs less frequently than hyaline pleural plaques and usually has a latent period of about 15-40 years. The morphology of diffuse pleural fibrosis is variable and depends on the severity of the disease. The visceral pleura is most frequently involved and shows varying degrees of whitish opacification. Microscopically, there is scarring, increased vascularity and inflammation. Occasionally, diffuse pleural fibrosis and hyaline pleural plaques co-exist. Some authors have suggested that visceral pleural fibrosis may be a direct extension of parenchymal fibrosis. If so, diffuse pleural fibrosis can be diagnosed radiographically as asbestosis, especially if there is underlying scarring of the lung parenchyma.

Occasionally, both the visceral pleura and the parietal pleura can scar to the point where they produce a condition referred to as *fibrothorax*, in which the lung is encased by a dense rind of fibrous tissue that macroscopically resembles mesothelioma, but microscopically is benign.

WR Grace Report   18

Round (rounded) atelectasis is a condition most frequently observed by radiologists in persons occupationally exposed to asbestos. Most persons who have round atelectasis are asymptomatic and, radiographically, have a unilateral, round, peripheral density often in the right lower and/or right middle lobes with one or more curvilinear shadows that radiate from this density towards the hilum of the lung. This lesion can be misinterpreted as a neoplasm. Various theories have been suggested with respect to the pathogenesis of round atelectasis.

Boutin et al. described black spots as areas where long amphibole fibers accumulated in association with carbonaceous dust and appeared black on the parietal pleura (Boutin C, Dumortier P, Rey F, et al. *Black spots concentrate oncogenic asbestos fibers in the parietal pleura: thoracoscopic and mineralogic study.* Am J Respir Care Med 1996 Jan;153(1):444-449). These were hypothesized to be the starting point for asbestos-related neoplastic and inflammatory conditions. Specifically, the authors suggested that mesothelioma originated in these black spots due to amphibole fibers. I have never seen a black spot on the parietal pleura of about 500 autopsies done on persons who were exposed to asbestos. If this reflects a different type of dust exposure in the United States versus elsewhere is uncertain.

Mitchev et al. evaluated the entire parietal pleura from 150 consecutive necropsies of urban dwellers for the prevalence, anatomic distribution and macroscopic appearance of black spots and hyaline pleural plaques (Mitchev K, Dumortier P, De Vuyst P. *Black spots and hyaline pleural plaques on the parietal pleura of 150 urban necropsy cases.* Am J Surg Pathol 2002;26:1198-1206). Black spots consisted of deposits of opaque particles located under and intact mesothelial layer often in association with chronic inflammatory cells; namely, plasma cells, lymphocytes and macrophages. They were stated to have been found predominantly in the lower paravertebral zones on the spine, or close to it, on the central tendenous parts of both diaphragms, and around the anterior axillary lines. They were stated to have been observed in 92.7% of cases and more frequently in males and those of advanced age. The authors concluded there was no correlation between the locations of anthracotic spots and pleural plaques. Pleural plaques were observed predominantly in areas of parietal pleura with a lower prevalence of black spots. Black spots were stated to be related to structures responsible for lymphatic drainage of the pleural cavity and specifically reflected "clogged sewage system," marking the places of maximal pleural re-absorption.

More recently, Muller et al. stated black spots were described to represent areas of coal dust accumulation with an increased incorporation of asbestos fibers (Muller KM, Schmitz I, Konstantinidis K. *Black spots of the parietal pleura: morphology and formal pathogenesis.* Respiration 2002;69:261-267). They evaluated the morphology and energy dispersive x-ray analysis of 12 black spots located in the parietal pleura. Black spots were stated to have developed in close correlation to lymphatic channels and blood vessels. Their formal pathogenesis was stated to have been characterized by a mild fibrosis and inflammatory reaction to the incorporated foreign particles. The proliferation of connective tissue could result in the formation of hyaline granulomas. Aluminum, silicone, and sometimes fibers were found in such areas and the mesothelial cells were stated to occasionally be irritated. The authors concluded that although there were hints for an increased proliferation of mesothelial cells in some areas with black spots, their findings did not support the classification of black spots as an obligate early lesion in the development of malignant mesothelioma.

Cases of severe pulmonary asbestosis in association with exposure to asbestos were described in the early 1900s. In 1924, Cooke coined the term "asbestosis" and published a detailed pathologic description of the disease. There have been several reports concerning the morphology of asbestosis. The term *pleural asbestosis* has sometimes been used to refer to

WR Grace Report

scarring of the pleura caused by asbestos and, in my opinion, this term should be avoided because it is confused with parenchymal scarring of the lung caused by asbestos, which is properly referred to as *asbestosis*. The macroscopic appearance of asbestosis depends on the severity of the disease. The disease has been categorized into four histologic grades - grade 1 being the least severe and grade 4 being the most severe.

Grade 0	No fibrosis is associated with bronchioles
Grade 1	Fibrosis involves wall of at least one respiratory bronchiole with or without extension into the septa of the immediately adjacent layer of alveoli; no fibrosis is present in more distant alveoli
Grade 2	Fibrosis appears as in grade 1 plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there still must be a zone of nonfibrotic alveolar septa between adjacent bronchioles
Grade 3	Fibrosis appears as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, fibrotic septa; some alveolar may be obliterated completely
Grade 4	Fibrosis appears as in grade 3, but with formation of new spaces of a size larger than alveoli ranging up to as much as 1 cm; this lesion has been termed *honeycombing*; spaces may or may not be lined by epithelium

The pathogenesis of asbestosis involves inflammation with release of various mediators that eventually stimulate the fibroblasts and interstitium of the lung to produce more collagen and elastin, which, if the disease is progressive, can over time obliterate the lung, resulting in diffuse interstitial fibrosis with honeycombing. It should be recognized there is a wide variation in the amount of asbestos one finds in the lung tissue of people with various grades of asbestosis. The reason for this is not well understood, but, like any other asbestos-related disease, there appears to be individual susceptibility to the development of the disease. The clinical features of asbestosis depend on its severity. Those with grade 3 and 4 asbestosis usually have significant shortness of breath and dyspnea on exertion and have distinct radiographic abnormalities. The primary differential diagnosis of asbestosis is idiopathic pulmonary fibrosis (usual interstitial pneumonia). Pathologically, there appears to be more fibroblastic foci in cases of usual interstitial pneumonia than there is asbestosis.

Since a significant percentage of individuals exposed to asbestos are also cigarette smokers, there has been some problem in determining the exact relationship between cigarette smoke and asbestos in causing interstitial fibrosis. Cigarette smoke has been found experimentally to inhibit clearance of asbestos in the lungs of guinea pigs. Cigarette smoke can also cause squamous metaplasia of the lining of the respiratory epithelium of the bronchi, which can inhibit clearance. Some studies have shown that cigarette smoke causes an increased penetration of amosite into the airway walls in guinea pigs resulting in an increased concentration of fibers in the interstitium.

With respect to radiographic abnormalities, cigarette smoke has been suggested to cause an increase in small irregular opacities, although other studies have not shown any increase. The 2004 ATS document on environmental and occupational health issues concerning asbestos-related diseases (American Thoracic Society Documents. *Diagnosis and initial management of nonmalignant diseases related to asbestos.* Am J Respir Crit Care Med 2004;170:691-715) stated that asbestosis was more prevalent and advanced for a given duration of exposure in cigarette smokers, presumably due to reduced clearance of asbestos fibers from the lung. Although some studies suggested that smokers without dust exposure showed occasionally

irregular radiographic opacities on chest films, smoking alone was stated to not cause changes of asbestosis. Therefore, smokers and ex-smokers were stated to have a higher frequency of asbestos-related opacities on their chest radiographs than did non-smoking asbestos workers in all profusion categories. The 2004 ATS document further stated cigarette smoking did not affect asbestos-induced pleural fibrosis.

As stated previously, the clinical features of asbestosis depend on the severity of the disease. Those with grade 3-4 asbestosis are usually symptomatic, with the most common symptom being dyspnea on exertion. There is an increased incidence of clubbing of the fingers, although the diagnostic usefulness of this finding is minimal. Most patients with pathologic grade 3-4 asbestosis have Velcro rales. Pulmonary function tests usually show restrictive lung disease with a decrease in total lung capacity and forced vital capacity. Hypoxemia may or may not be present at rest, or may develop with exercise, and the diffusing capacity is usually decreased.

In 1986 the American Thoracic Society (ATS) proposed the following criteria for the clinical diagnosis of asbestosis: 1) a reliable history of exposure to asbestos; 2) an appropriate latent interval between exposure and detection of asbestosis; 3) chest roentgenographic evidence of type "s," "t" or "u" small irregular opacities with a profusion of 1/1 or greater; 4) a restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal; 5) a diffusing capacity below the lower limit of normal; and 6) bilateral or late pan inspiratory crackles at the posterior lung bases not cleared by coughing. In 2004, the ATS document lists the criteria for diagnosing lung diseases, including asbestosis, and commented on the 1986 criteria. This is shown in the table below. In 2004 the ATS stated that a profusion of irregular opacities at the level of 1/0 is used as the boundary between normal and abnormal.

Table 27–15. Criteria for diagnosis of nonmalignant lung disease related to asbestos.
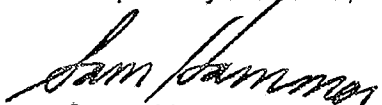
1986 Guidelines	2004 Guidelines	Comparison and Notes
	Evidence of structural change, as demonstrated by one or more of the following:	Demonstrates the existence of a structural lesion consistent with the effects of asbestos. The criteria outlined in the 1986 guidelines were most explicit for asbestosis.
Chest film (irregular opacities)	• Imaging methods	Chest film, HRCT, and possibly future methods based on imaging. The 1986 guidelines specified ILO classification 1/1.
Pathology (College of American Pathologists)	• Histology (College of American Pathologists)	Criteria for identifying asbestosis on microscopic examination of tissue are unchanged.
Consistent time interval	Evidence of plausible causation, as demonstrated by one or more of the following:	
Occupational and environmental history	• Occupational and environmental history of exposure (with plausible latency)	
	• Markers of exposure (e.g., pleural plaques)	
Asbestos bodies or fibers in lung tissue	• Recovery of asbestos bodies	The 2004 guidelines are not limited to lung tissue, consider the role of BAL to be established, and deemphasize fibers because they are difficult to detect and a systematic analysis for asbestos fibers is not generally available.
Rule out other causes of interstitial fibrosis or obstructive disease	Exclusion of alternative diagnoses	The 1986 guidelines primarily addressed asbestosis but mentioned smoking as a cause of obstructive disease. Implicit in the article, however, is that nonmalignant diseases presenting similarly to asbestos-related disease should also be ruled out.
"Evidence of abnormal test"	Evidence of functional impairment, as demonstrated by one or more of the following:	Functional assessment is not required for diagnosis but is part of a complete evaluation. It contributes to

WR Grace Report

		diagnosis in defining the activity of disease and the resulting impairment.
Crackles, bilateral, not cleared by cough	• Signs and symptoms (including crackles)	Signs and symptoms are not specific for diagnosis but are valuable in assessing impairment.
Restrictive disease	• Change in ventilatory function (restrictive, obstructive patterns in context or disease history)	The 1986 criteria admitted the possibility of obstructive disease; the 2004 criteria address this specifically.
Reduced diffusing capacity	• Impaired gas exchange (e.g., reduced diffusing capacity) • Inflammation (e.g., by bronchoalveolar lavage)	The 1986 guidelines noted possible utility of bronchoalveolar lavage and gallium scanning but considered them to be experimental techniques. The 2004 guidelines exclude gallium scanning, suggest that additional indicators of active inflammation may become useful in future.
	• Exercise testing	

Kipen et al. stated that of 400 confirmed deaths from lung cancer, a chest radiograph suitable for determining evidence of pneumoconiosis was obtainable in 219 (Kipen HM, Lilis R, Suzuki Y, et al. *Pulmonary fibrosis in asbestos insulation workers with lung cancer: a radiological and histopathological evaluation*. Br J Ind Med 1987;44:96-100). Of these cases, 138 also had a tissue specimen that was suitable for histologic study to determine the extent of histological fibrosis. There was stated to be a significant, albeit limited correlation between the radiographic and histologic findings (r = 0.27, p < 0.0013). All 138 cases had histologic evidence of parenchymal fibrosis. In 25 cases (18%), there was no radiographic evidence of parenchymal fibrosis. In 10 cases (7%), both parenchymal and pleural disease were undetectable on the radiograph. The authors concluded a negative chest radiograph does not exclude the presence of interstitial fibrosis (asbestosis) in a substantial proportion of insulation workers previously exposed to asbestos who developed lung cancer. This study should be kept in mind, especially in people who are symptomatic and whose chest radiographs do not show changes suggestive of asbestosis.

Localized and unusual pulmonary diseases occur in persons occupationally exposed to asbestos. These include organizing pneumonia-bronchiolitis obliterans (BOOP); desquamative interstitial pneumonitis-like change; asbestos-cigarette smoke-induced interstitial lung disease; aspergillus infection in asbestos-exposed individuals; granulomatous inflammatory-type changes; and lymphocytic interstitial pneumonia. In the 2004 ATS document, they referred to the organizing pneumonia-type changes as asbestomas. These are usually misinterpreted radiographically as lung cancers and, perhaps not surprisingly, they show an increased activity when evaluated by positron emission tomography (PET scans).

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Curriculum Vitae
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PERSONAL

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EDUCATION

Board Certified Anatomic and Clinical Pathology: May 1975

Post-Doctorate Training:

Straight Pathology Internship -- University Hospital, Seattle, Washington; July 1969 - June 1970.

Pathology Residency -- University of Washington Affiliated Residency Program, Seattle, Washington; July 1970 - September 1973

Experimental Pathology Training -- University of Washington Pathology Department; under the direction of N. Karle Mottet, M.D.; July 1971 - July 1972.

Electron Microscopy Training -- University of Washington Pathology Department; under the direction of Dr. Greta Tyson and Russell Ross; July 1972 - December 1972.

Medical School: University of Washington Medical School, Seattle, Washington, 1965 - 1969; earned M.D. degree.

Undergraduate College: Eastern Washington State College, 1961 - 1965; earned BA degree in chemistry.

POSITIONS HELD

Director, Diagnostic Specialties Laboratories, Inc., Bremerton, Washington, February 1989 to present.

Pathologist, Pathology Associates of Kitsap County, Harrison Memorial Hospital, Bremerton, Washington, February 1989 to present.

Panel for the reclassification of lung tumors, World Health Organization (IASLC Panel), 1995 - present.

Reviewing Pathologist, U.S. and Canadian Mesothelioma Panel, February 1988 to present.

Clinical Professor of Pathology, University of Washington School of Medicine, 1990 to present.

Reviewing Pathologist, CARET Study (Carotene and Retinoic Acid Efficacy Trial); Fred Hutchinson Cancer Research Center, Seattle, Washington.

Clinical Associate Professor of Pathology, University of Washington School of Medicine, 1984 to 1990.

Chairman, Institutional Review Board, Virginia Mason Medical Center, 1984 - 1988.

Pathology Chairman, Pathology Reference Center Library, Lung Cancer Study Group, 1980 - 1989.

Pathologist, Virginia Mason Clinic, Seattle, Washington, September 1975 to January 1989.

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CV page -2-

Assistant Professor, Department of Pathology, University of Utah College of Medicine; Director, Electron Microscopy, Veterans Administration Hospital, Salt Lake City, Utah, October 1973 to August 1975.

Chief Resident, Department of Pathology, University Hospital, Seattle, Washington; July 1971 to August 1973.

HONORS AND AWARDS

Senior medical student thesis honors award. June, 1969.

Sheard-Sanford Award from the American Association of Clinical Pathology for meritorious student research. June, 1969.

National Foundation Award for the best original student research in the field of birth defects. June, 1969.

Outstanding Instructor in Pathology, University of Utah School of Medicine. 1975.

SOCIETY MEMBERSHIPS

American Association of Pathologists
International Academy of Pathology
American Thoracic Society
American Society of Clinical Pathology
American Society of Experimental Biology
American Medical Association
Washington State Medical Association
Pacific Northwest Society of Pathology
King County Medical Society
American College of Chest Physicians
Society for Ultrastructural Pathology
Society for Pulmonary Pathology

PUBLICATIONS

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8. Tolan KG, Hammar SP, Sanella JJ. *Possible hepatotoxicity of Doxidan.* Ann Int Med 1976; 84:290-292.
9. Bowers J, Koehler PR, Hammar SP, et al. *Rupture of a splenic artery aneurysm into the pancreatic duct.* Gastroent. 1976; 70:1152-1155.
10. O'Neill W, Hammar SP, Bloomer, HA. *Giant cell arteritis with visceral angiitis.* Arch Int Med 1976; 136:1157-1160.
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13. Kanner RE, Hammar SP. *Chronic eosinophilic pneumonia: ultrastructural evidence of marked immunoglobulin production plus macrophage ingestion of eosinophils and eosinophil lysosomes leading to intracytoplasmic Charcot-Leyden crystals.* Chest 1977; 71:95-98.
14. Lynch, RE, Hammar SP, Lee GR, Cartwright GE. *The anemia of vitamin E deficiency in swine: an experimental model of the human congenital dyserythropoietic anemias.* Am J Hematol 1977; 2:145-158.
15. Hammar SP, Gortner D, Sumida S, Bockus D. *Lymphomatoid granulomatosis: association with retroperitoneal fibrosis and evidence of impaired cell mediated immunity.* Am Rev Resp Dis 1977; 115:1045-1050.
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85. Hammar SP, Hallman KO. *Localized inflammatory pulmonary disease in subjects occupationally exposed to asbestos.* Chest 1993; 103:1792-1799.

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87. Hammar SP. *The pathology of benign and malignant pleural disease.* Chest Surg Clin N Amer 1994; 4(3):405-430.

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